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SCIENCE AND SOCIETY

Opportunities for cancer epidemiology in developing countries

Tanuja Rastogi, Allan Hildesheim and Rashmi Sinha

Abstract | Most cancer epidemiology studies involve people living in North America and Europe, which represent only a fraction of the global population. The wide variety of dietary, lifestyle and environmental exposures, as well as the genetic variation among people in developing countries can provide valuable new information on factors that contribute to cancer or that protect against it. What are the challenges and advantages to performing large epidemiological studies in developing nations?

The incidence of cancer and other chronic diseases is increasing in developing countries owing to increased life expectancy and changes in risk factors that are concomitant with economic development. The dramatic improvements in life expectancy that are observed in middle-income countries can be attributed to better public health practices such as immunization and improved nutrition. This has reduced infant and child mortalities from infectious diseases and malnutrition. By contrast, according to the World Health Organization, mortality from cancer is expected to increase considerably in developing countries including Asia, Africa and Latin America (FIG. 1). Although cancer incidence rates are still substantially lower in developing countries than in developed countries, the burden of cancer and other chronic diseases pose an important threat to already overwhelmed health-care systems.

Changes in lifestyle and diet that occur with economic development typically include unhealthy practices such as sedentary behaviour, smoking, increased total energy intake and consumption of highly refined foods, sugars, saturated fat and meats. These adaptations are due, in part, to the mechanization and modernization of processes ranging from transportation to household chores. Additionally there is increasing availability and demand for cheaper food options, which tend to be high in both fat and sodium and low in fibre. Such adaptations are often referred to as 'Westernization' — the umbrella term that encompasses these behaviours, which are common in North America and parts of Europe.

Most of the research into cancer has been done on people living in North America and Europe, representing only a fraction of the global population and their dietary patterns and lifestyle factors. The wide variety of diet, lifestyle and environmental exposures, as well as genetic variation between populations in developing countries, can add valuable information to our knowledge of the factors that contribute to the development of cancer. The international portfolio of cancer studies therefore needs to be expanded to developing countries. These types of studies would not only serve the needs of people in developing countries, but also progress our overall knowledge of cancer aetiology. There are, however, many logistical issues that need to be addressed when performing epidemiological studies in developing nations. These include defining research priorities by taking into consideration past scientific discoveries so that efforts are not unnecessarily repeated and limited resources are preserved. Furthermore, key infrastructure requirements need to be considered, as well as strengthening the epidemiological research capabilities of institutions in developing countries.

Regional variation in cancer incidence

Incidence of cancer varies dramatically between geographic regions (FIG. 2); as some cancers are more common in people in the developed world (for example, breast and prostate), others occur more frequently in people who live in developing countries (for example, cervical and stomach). Cancers of the lung have high incidence in both developed countries and areas undergoing economic development such as China[1]. Although these regional differences might be explained by genetic differences among populations, variations in lifestyles, environmental exposures and medical practices such as screening are also likely to be important determinants of cancer risk. This assumption is reinforced by migration patterns that show that incidence of cancer among migrants changes to more closely reflect the rates in the adoptive country. This has been observed

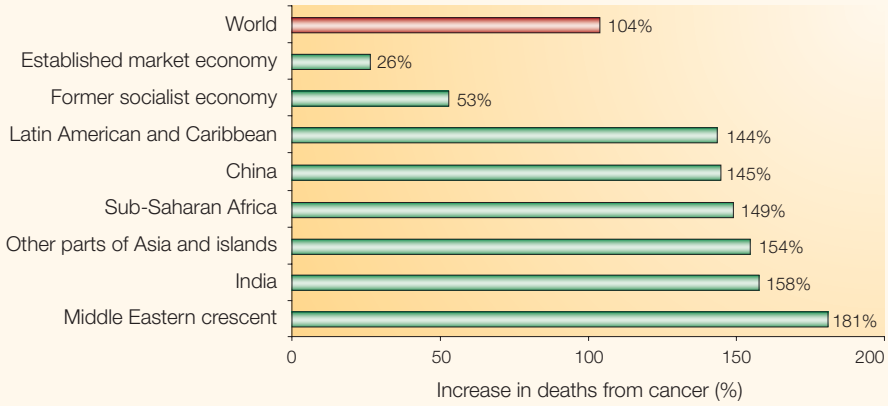


Figure 1 | **Changes in cancer mortality by region.** According to the World Health Organization, death from cancer is expected to increase 104% worldwide by the year 2020. The largest increases are predicted to occur among people living in developing countries (Latin America, the Caribbean, Asia, the Middle East and Africa) in comparison with those in developed countries (established market economies and the former Soviet economy). Although actual cancer incidence rates are still lower in developing countries than in North America and Europe, the rise in cancer-related deaths will represent a significant burden to the already overwhelmed health systems in developing countries. Data taken from REF. 53.

with the incidence of colon cancer in Japanese people emigrating to Hawaii and San Francisco[2]. Additionally, the incidence of prostate and breast cancers are low among Chinese people in Asia, but increases have been observed when these people move to the United States of America[3]. Dramatic increases in cancer incidence have also occurred within countries that experienced massive economic development in the past 50 years[1]. For instance, younger generations of Japanese (born after 1930) now have a similar if not greater incidence of colorectal cancers than their US Caucasian counterparts[4]. So as lifestyles also change in developing countries, we are likely to see a significant rise in the incidence of cancers that have previously been associated with developed countries, such as breast, colon, prostate and lung cancers.

Both environment and genetic variation are important factors in the aetiology of many chronic diseases. Genetic variation causes many metabolic differences between individuals, and there is much interest in understanding the potential impact of this variation on susceptibility to cancer and cancer pathogenesis. Specific mutations in single genes have been reported to greatly increase the risk of some types of cancer, although the prevalence of these mutations is rare at a population level. By contrast, common genetic polymorphisms that contribute only a modest variation in risk can have a greater impact on public health, especially in conjunction with environmental exposures.

Understanding these gene–environment interactions is one of the main challenges in unravelling the aetiology of cancer and other complex diseases. One approach is to study the risks of cancer in different populations in different environments. Population studies that collect data from different races incorporate global variability in both genes and environmental factors such as different diets, tobacco or pesticide exposures, and they therefore have enormous potential in expanding our understanding of mechanisms involved in carcinogenesis.

Research potential

Developing countries have unique features that make them important to include in studies of the environmental and genetic factors that contribute to cancer risk.

Specific exposures. People living in developing countries or geographic regions outside of North America or Europe are exposed to different environmental factors than people in the Western world. Some examples include arsenic in tube-well water of the Indo-Gangatic plains, or exposure to radon, which is produced naturally from the earth, in specific regions of China. There are also many dietary variations, especially among populations in Asia, Africa or Latin America, that might be associated with disease risk. Turmeric, a yellow-colour spice and flavour commonly consumed by millions of people, particularly in South Asia, has traditionally been used as a remedy for liver ailments. Curcumin, a constituent of turmeric, is a phytochemical that is currently being researched for its anti-tumour properties, such as inducing cell-growth inhibition and apoptosis. Research on these and other region-specific exposures can expand our understanding of cancer epidemiology beyond what has been gained from developed countries.

Exposure to a wider range of factors. The homogeneity (narrow range) of lifestyles and environmental exposures among people living in developed nations has resulted in an incomplete understanding of the relationship between many factors and cancer risk. People living in developing countries can be exposed to a wider range of environmental factors. The developing world consists of many countries with populations that are ethnically, culturally and socially different from each other. Ranges in lifestyle and exposures are further widened by dramatic socioeconomic differences of populations in countries where both 'rich and poor' subgroups coexist together. Factors that might make only a small contribution to cancer risk, such as fat or fibre intake, are easier to detect over this greater range, as sometimes their contribution to cancer risk can only be detected at very high or low exposure levels.

Changing patterns. Changes in lifestyles and environmental exposures can be associated with an increase or decrease in disease risk, providing useful clues for aetiological studies. Epidemiological studies that correlate increased or decreased exposure to certain environmental factors with cancer risk need to be carried out quickly, as many people worldwide are rapidly adopting 'Western' lifestyles. Although not all segments of populations in developing countries are undergoing such changes, it is plainly visible that others, particularly urban populations, are increasing their consumption of fast, energy-dense but nutrient-poor foods, and sedentary lifestyles are becoming the norm. Studies of these populations can be used to determine which of these factors might contribute to certain types of cancer.

Patterns of confounding factors. 'Confounding' is a major challenge to studies examining the association between multiple exposures and risk of disease. When two variables are highly correlated and are both associated with disease risk, it is difficult to separate them and determine which variable is involved in disease pathogenesis. If an association between a specific factor and disease can be reproduced in populations with different confounder and correlation structures, it is more likely be considered 'significant'. For example, studies

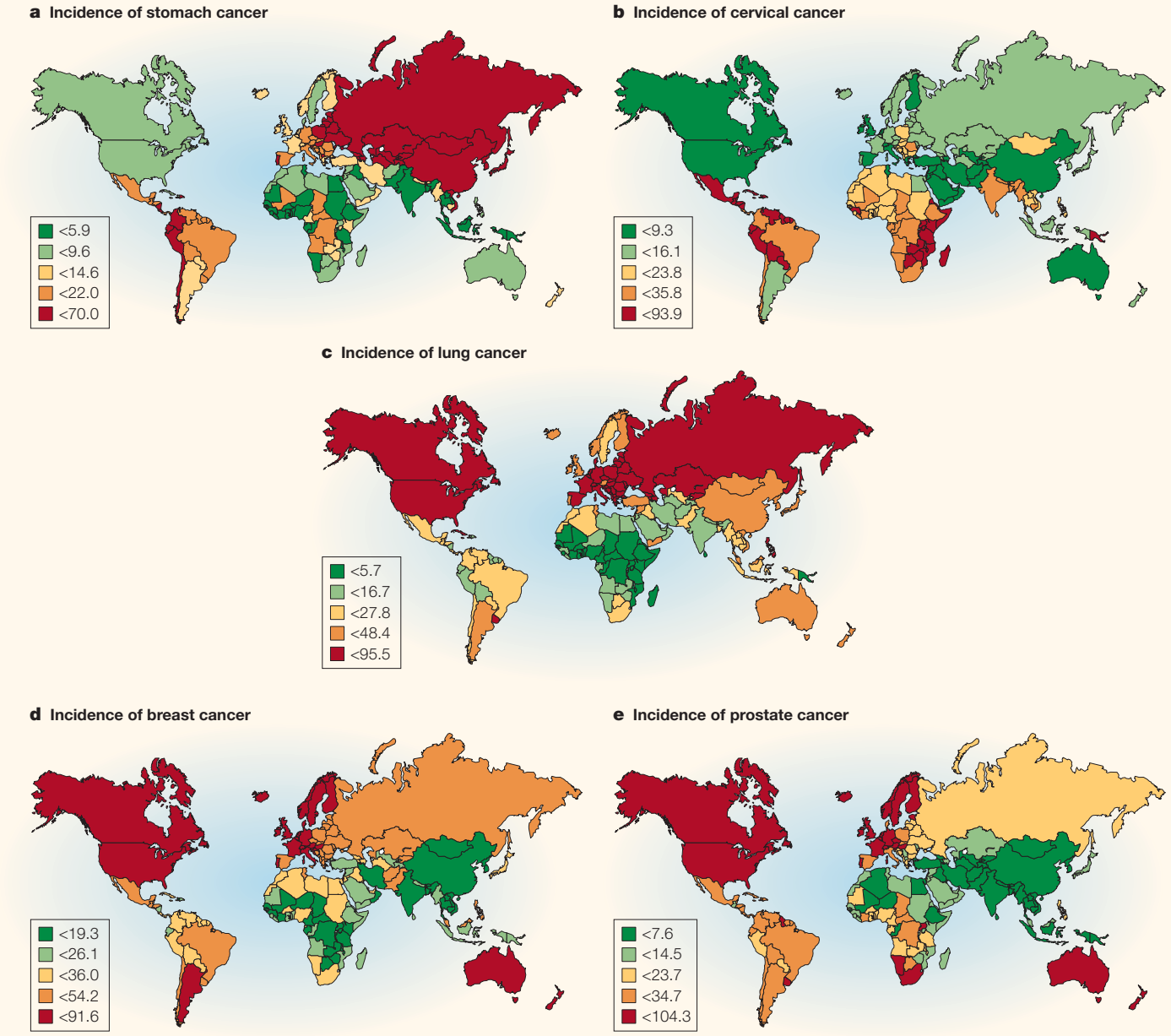


Figure 2 | **Global variations in cancer incidence for specific cancers.** There is substantial global variability in cancer incidence (measured as age-standardized rates) occurring in people living in developing countries (**a**–**c**) and those in developed nations (**d**,**e**). **a** | The incidence of stomach cancer for men of all ages is highest (orange and red) in developing countries such as Asia and South America, and lowest (light and dark green) in North America, parts of Africa, India and Australia. **b** | The incidence of cervical cancer is also high in developing regions of the world including Latin America, Africa and India, and is low (green) in North America, Europe and Australia. **c** | Lung cancer incidence is currently high in developed countries as well as those countries undergoing economic transition, such as China. **d**,**e** | Cancers with the highest incidence in developed countries include breast and prostate cancer, which occur most commonly in North America, Europe and Australia, and with much lower incidence in Asia and Africa. These differences highlight the role that environmental and lifestyle factors such as diet have in cancer development. Data from REF. 54.

into the effects of vegetarianism are generally confounded by other aspects of an overall healthy lifestyle among Western populations, such as higher amounts of exercise and lower alcohol and tobacco use. In India, however, people are vegetarians for religious reasons and are otherwise likely to have similar lifestyles to the rest of the population. Also, in developed countries, factors such as increased physical activity are confounded by factors such as higher socio-economic status, which is also related to better health. However, poorer groups tend to be more active in developing countries. The effects of physical activity on cancer risk can therefore be more clearly evaluated by assessing data from both developed and developing countries.

Accuracy in assessment. Another challenge to epidemiological studies of environmental factors and disease risk is measuring levels of exposure to a given agent. Error in diet assessment, for instance, has long been recognized as a potentially serious problem in nutritional epidemiological research that can substantially attenuate risk estimates. Problems in accurately determining food intake might

Table 1 | **Dietary factors to examine in developing countries***

Dietary factor	Region	Cancer risk
Meat — overall intake, specific specific types of meat, cooking methods, fat content, intake of processed meats	South and Central America, China	Colorectal cancer (potential)
Soy	Southeast Asia	Breast cancer (potential)
Pulses, lentils and beans	Central and South America, South Asia, Africa	NS
Vegetarian diets	South Asia	Colorectal and other cancers (potential)
Micronutrient deficient — carbohydrate-dense diets	Rural Asia and Africa	NS
Allium vegetables	East Asia	Colorectal and prostate cancers (potential)
Spices (for example, curcumin in turmeric)	South and Southeast Asia, Caribbean	Colorectal cancer (potential)
Vegetable oils: palm oil, coconut oil, rapeseed/flaxseed oils, and trans fatty acids in hydrogenated oils	Eastern Europe, South and Southeast Asia	NS

*See ref. 15. NS, not studied; there is currently no information available on how these diet components influence risk.

account for some of the inconsistency in the nutrition and cancer research from North America and Europe. Estimating food consumption in developing countries might be easier, as food represents a larger percent of total expenses and is usually prepared at home. Preliminary evidence indicates that dietary assessment error might be lower in India[5]. Other researchers have speculated that recall of physical activity among Chinese is more likely to be accurately reported, as major forms of energy expenditure are not leisure-time but transportation or occupation-related activities, such as bicycling to work. Such essential activities are done on a daily basis and can be more accurately recalled, thereby reducing measurement error.

Cancer-related factors to be studied

There are so many advantages to performing epidemiological studies in the developing world, but which environmental factors are most important to evaluate immediately for association with cancer risk?

Diet. So far, much of the diet and cancer research conducted in developing nations has focused on specific diet components. For example, studies in South and Southeast Asia have elucidated the association between oral cancer and intake of areca nut — the seed of the betel palm that is chewed with leaves of the betel pepper and lime as a digestive stimulant and narcotic in southeastern Asia[6–8]. This nut has been found to be carcinogenic even when consumed without tobacco. Also, intake of foods with high salt contents such as salty fish, which is consumed in high levels in several East Asian countries, has been associated with gastric cancer incidence in China, Japan and Korea[9–14].

In their report, *Food, Nutrition and the Prevention of Cancer: A Global Perspective*, an international panel of experts recommended that comprehensive dietary studies should be conducted in diverse populations, including those that consume low and high levels of plant proteins, cereal intake, starchy roots and tubers, and bioactive components of vegetarian diets and spices[15]. In TABLE 1 we list certain dietary components that are associated with specific populations and that have not been previously studied extensively. Little is known about how many of these dietary components influence cancer risk. It is therefore important to study a range of diets consumed by the world's population to gain a broader understanding of its relation with the disease process — only analyzing diets of North Americans and Europeans provides a limited view of how diet can increase or decrease risk.

Infectious agents. Approximately 20% of cancers among men and women in developing countries are attributable to infectious agents, compared with 9% in developed countries[16]. Advances in our understanding of cancer mechanisms have therefore been made by studying infectious disease-related cancers in developing countries. The role of HPV (human papilloma virus) infection in cervical cancer aetiology has been clearly demonstrated through epidemiological investigations in developing countries such as Asia, Africa and Latin America[17–19]. Also, *helicobacter pylori* infection has been associated with a two- to three-fold elevation in risk for stomach cancer in epidemiological investigations[20]. Studies on hepatocellular carcinoma from Asia and Africa indicate that persistent hepatitis B infection and aflatoxin exposure can act synergistically to increase cancer risk[21–25]. So for infectious disease-related cancers, we are now at the next stage of research where attention is focused on how to prevent cancer-causing infections. Novel screening strategies and vaccines are already being developed for cervical cancer prevention that is caused by HPV[26]. Also, studies in Taiwan have reported reduced rates of hepatocellular carcinoma after widespread vaccination of children against hepatitis B[27]. Other key areas of infectious disease research that need to be expanded include surveillance for both infection with a particular agent and for cancer, as well as the effects of promoting cancer prevention programmes. For a list of other agents that contribute to cancer pathogenesis, see TABLE 2.

Environmental and occupational exposures. People in developing countries are exposed to broader ranges of occupational and environmental hazards, as more people are involved in manufacturing, farming, mining or other industrial occupations than developed nations. Research in China, for instance, has shown a positive association between lung cancer and radon gas exposure[28], which is high in some homes and among underground miners. In both China and India, indoor air pollution due to burning of coal and biomass for cooking and heating in homes has also been associated with lung cancer[29–34]. Studies are also underway to analyse levels of arsenic, which has been associated with bladder and lung cancers, in the drinking water in Bangladesh, India, Chile, Taiwan and China[35–41]. Further research in these areas might provide important and unique information that cannot be gained from studies in the developed world and ultimately used in cancer-prevention efforts.

The prevalence of tobacco smoking, clearly an important risk factor for cancer, is high in developing countries, with over 80% of the world's smokers living in low- or middle-income countries, and a disproportionately high number of these people being in East Asia[42]. Moreover, the forms of tobacco that are used vary in developing countries. Smoking of bidis — small unfiltered cigarettes that are hand-rolled in a temburni leaf — and chewing

tobacco are particularly common among lower-income groups of Asia. It will also be important to study the interaction between tobacco use and other features of developing countries, such as the high incidence of tuberculosis, indoor air pollution and radon exposure. Furthermore, in developing countries there is much need for public health education on the risks of tobacco use, so this data can be used to support government policies designed to reduce tobacco use.

Another major environmental and occupational factor that contributes to lung cancer risk is fuel exhaust, which contains diesel particles and polycyclic aromatic hydrocarbons[43]. This association is not well-studied in developing countries, where exhaust levels are high. The interactions between exhaust and other lung carcinogens, such as tobacco use, radon or silica, can also be examined. The use of pesticides has also increased drastically in developing countries over the last three decades, owing to increased crop production[44]. These chemicals have been associated with leukaemia, lymphoma and prostate cancer risk[45], and represent important areas for further research. Studies investigating benzene exposure of workers in the shoe and paint industries, which are common in developing countries[46], can provide information about the dose-response relationship between benzene and cancers such as lymphoma, leukaemia and even lung cancer. Moreover, aromatic amines are still extensively used in various industries for textile dye and rubber making in India, China and Southeast Asia. Research into the association between these compounds and cancer might expand our understanding of its potential role in bladder cancer.

Physical activity. Research in developing countries on the association between physical activity and cancer can provide valuable information on the magnitudes and types of activities that can protect people from cancer. Although there have been many studies into the affects of physical activity, energy balance and obesity on disease incidence in North America and Europe, these types of studies should be expanded to developing countries. Both the level and type of physical activity vary dramatically between developed and developing countries. Main sources of energy expenditure in economically developed countries are derived from leisure-time exercise, which is a focus of both research and health promotion. Studies in China, India and Brazil indicate that the main forms of energy expenditure arise from occupation and transportation-related activities, as well as chores and other types of non-leisure-related exercise[47–49]. Additionally, levels of physical activity might have wider ranges in developing nations, owing to the diversity of activities undertaken and because of the dramatic differences of 'rich and poor' subgroups within the same population

Hormones. Developing countries provide many opportunities to examine a number of unique hormonally-related variables. For example, they can address the effects of wider ranges in body sizes — from underweight to obese — which in addition to physical activity are believed to affect cancer risk by modulating hormone levels. Excess body weight or increases in abdominal fat have been reported to alter serum levels of insulin and insulin-like growth factor-1 (IGF1), which function to stimulate cell proliferation, inhibit apoptosis and promote angiogenesis[50,51]. Moreover, weight gain often results in insulin resistance, leading to further production of insulin by the pancreas. Cancer researchers are currently examining the association between obesity-related increased insulin levels and insulin resistance with risk of colon, prostate, breast and pancreatic cancer[50]. Adiposity is also thought to influence risk of breast cancer among post-menopausal women and endometrial cancer by increasing circulating oestrogen levels[51]. Reproductive factors also modulate oestrogen levels and can influence cancer risk. These factors include total lifetime oestrogen exposure, the time span from menarche to menopause, parity, lactation and age at first birth.

Studies in countries such as Brazil and India provide opportunities to better understand these mechanisms, as the prevalence of overweight and obesity is rising, if not high already, among certain segments of the population. Different populations often have varying body shapes — for example, the prevalence of central obesity is particularly high among South Asians. Compared with Western nations, there are also significant differences in reproductive patterns among people in developing nations, where traditional segments of the population tend to have more children at younger ages. This is in juxtaposition with women in major urban regions who are employed and have fewer children at later ages, which is more typical of the Western world. These variations provide a potentially rich opportunity to compare how differences in parity contribute to hormone-related breast and endometrial cancers.

Table 2 | **Environmental factors and cancer risk in developing countries**

Cancer type	Regions	Environmental factors that increase risk	References
Cervical	Asia, Africa, Latin America	Human papilloma virus	17–19
Liver	Egypt, East Asia, Africa	Hepatitis B and C virus, aflatoxin	21–25
Oral	India, Southeast Asia	Areca nut, tobacco chewing	6–8,55,56
Stomach	China, Japan, Korea, Chile	Salt, high intake of salty foods, salty fish, *Helicobacter pylori* infection	9–14,20,57
Lung	China, India,	Radon exposure, indoor air pollution, tobacco smoking	28–34,58,59
Thyroid	India	Radiation exposure	60

Challenges

For cancer epidemiology research to be supported and sustained in developing countries, specific issues such as the development of infrastructure, strengthening of the epidemiological research capabilities, and the fostering of fair and effective collaborations must be addressed. Establishing all or even some of these factors can be major undertakings in regions where the capacity for cancer research is in a formative stage.

Infrastructure. The challenges that are faced in physical infrastructure involve improving the quality of epidemiological data that is collected, as well as improving systems for biological specimen collection, processing and storage. The existence of many basic elements, such as registries to determine disease incidence or mortality data, or surveys of environmental exposures, might require implementation. Population studies of cancer incidence will become logistically easier as improvements are made in access to medical care, diagnostics, laboratories and record/registry systems. There are some health-care systems already in place in developing countries that can be used as models, such as vaccination programs or national nutrition surveys. The information gained from these established infrastructures can be used in setting up epidemiological population-based studies and cancer screening programs.

Table 3 | **Epidemiological study designs**

Study type	Time frame	Basic design	Sample size	Data and samples collected	Knowledge gained
Cross-sectional survey	Short term	One-time data collection	Tens to thousands	Questionnaire, biological samples*	Population distribution of exposures (for example, intake of vegetables, serum cholesterol levels, prevalence of genetic polymorphisms)
Case-control study	Several years	Retrospective design. Compare risk factors of cases with disease and controls without disease	Hundreds to possibly thousands	Questionnaire, biological samples*‡	Questionnaire data and biological measures compared between diseased and non-diseased people. Case-control bias, where it is possible that disease status affects questionnaire responses or biomarker levels is a concern. Biomarkers with a long half-life (for example, adipose fatty-acid levels) and genetic polymorphisms might not be influenced by this bias
Cohort study	Decades	Prospective design. Cause-effect examined with a temporal sequence of events. Healthy subjects provide information (for example, diet, occupation, medical history, and so on) and are then followed for health-related events (for example, cancer, heart disease, diabetes) for a given period of time	Thousands to tens of thousands	Questionnaire, biological samples*	Questionnaire data and biomarker levels are useful (without biases inherent in case-control studies) and compared between people who develop disease and those who remain disease-free
Clinical trials	Variable	Prospective evaluation of specific intervention optimally randomized where subjects and investigators are blinded to the treatment status	Tens to thousands	Exposure is determined by the investigator and is controlled (for example, vitamin E supplementation, vaccine trial). Repeated biological sample collection to assess effect of intervention	Efficacy of intervention evaluated based on biomarker levels and/or disease or intermediate status of disease (for example, effect of dietary fat and fibre intake on colorectal cancer or polyp occurrence).

*An array of biological samples are used in epidemiological studies and include the following examples: blood components, saliva/buccal cells from mouthwash, urine, faeces, nails, hair, and more invasive samples include biopsies of adipose tissue, rectal biopsies or tumour blocks. DNA for use in genetic analyses can be extracted from blood and buccal cells as well as from tumour blocks. ‡Use of biological samples in case-control studies need to be carefully evaluated as disease status might substantially effect biological measures.

Important factors for conducting prospective cohort studies include being able to link cancer registry data with study subjects and the ability to follow up subjects to obtain additional information on exposure and possibly outcome that is not usually available through registries. For a list of the various features of different study designs, see TABLE 3. Developed countries generally have high-quality national registries that record cancer incidence and mortality data, such as the US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database. The situation varies among developing countries — some areas such as Shanghai, China, already have well-linked population-based cancer registries, whereas other countries have few or no records of cancer incidence.

Patient follow-up is also difficult in some populations. It is important that individuals that participate in a prospective cohort study (TABLE 3) are not 'lost' over the course of the study (loss to follow-up), as no disease information would be available. Follow-up is difficult in populations that are transient, such as migrant groups or labourers who shift from one geographic region to the next in search of employment. Failure to follow participants carefully can bias the study results if the loss primarily occurs in one particular population that has different exposures or disease incidence than the others. For example, the likelihood of follow-up of individuals in slums or shanty towns in developing countries is low, as these areas are often unplanned and lack official addresses. As individuals living in slums also have less access to health care, cancer cases would more often go undiagnosed and would never be recorded in a cancer registry in comparison with middle-income participants. In a study that obtains cancer outcome data solely from cancer registries, data would incorrectly show that participants living in slums have lower incidence of cancer than the middle-income subjects. As the diets and lifestyles of people living in these deprived areas differ significantly from those of middle-class participants, the loss to follow-up can bias any observed association between particular dietary factors and cancer incidence.

Another obstacle that is faced by epidemiological studies in developing countries is that, owing to high illiteracy levels and lack of official addresses among certain segments of the population, follow-up might be difficult — particularly when mailed questionnaires are involved. This can be addressed, in part, by having researchers visit households to collect both exposure and outcome data. Whereas trained, non-medical research assistants can be appropriate in some locations, research nurses or paramedical technicians might be required in others. One advantage to studies carried out in developing nations is that in-person home interviews can cost substantially less than they would in developed nations, where this research approach is prohibitively expensive owing to higher labour costs. Information obtained through household visits can also be supplemented with medical records, doctor's reports and laboratory test results, if available.

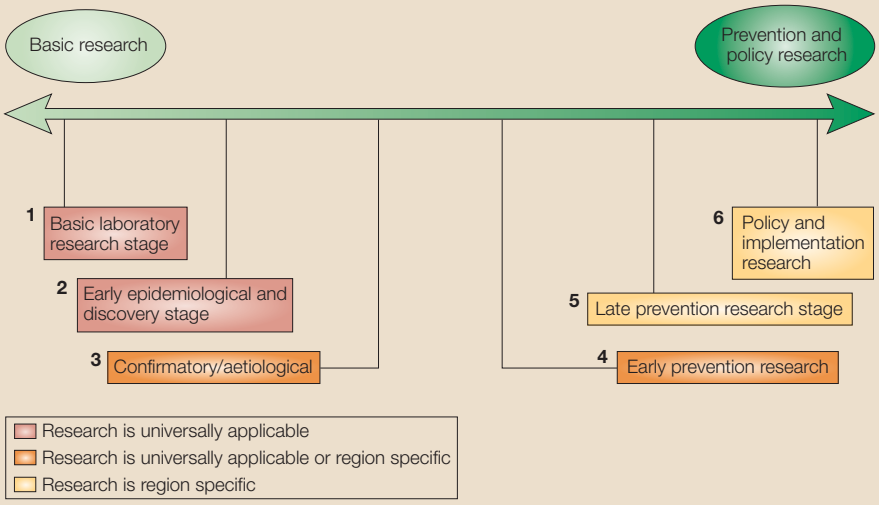
Obtaining accurate cause-specific mortality information from death registries is often difficult in some developing countries owing to incomplete death reports, and is especially important for prospective cohort studies, in which both cancer incidence and mortality are assessed. Death registry data can often be supplemented with questionnaires that are given to the next-of-kin of deceased study participants. Providing family members with questionnaires about the deceased individual's symptoms and signs of illness can be an alternate method for tracking causes of death in developing countries[52]. However, the accuracy and validity of these questionnaires should be evaluated in known study populations before implementation. Retrieving medical records of deceased study participants is important, particularly for determining the type of cancer that the deceased individual had.

Biological sample collection is another integral part of any epidemiological study, but is also a challenge in developing nations. Specimen collection in hospital-based case-control studies can be easily managed, whereas population-based samples are much more difficult to collect. Compliance can be low when subjects are recruited from the general population, especially for blood collection. Even if subjects agree to give blood, the amount might be minute, so more sensitive laboratory methodologies or other types of biological specimen collection (blood spots, DNA from mouthwash) need to be developed. Education or appropriate incentives can increase participation. Other challenges involve the storage of samples at the appropriate temperature, transport to the processing centre, correct processing and long-term storage, which can be expensive. So without a functional infrastructure, it is not always possible to carry out certain types of epidemiological studies in developing nations.

Box 1 | **Continuum of research**

Research into risk factors associated with cancer develops along a continuum that spans from basic laboratory to epidemiological and, ultimately, prevention/policy research. The stages of research development generally include basic laboratory research, early epidemiology and discovery-stage studies, aetiological studies in humans, prevention studies, late-stage prevention studies and, ultimately, policy and implementation research. Whereas prevention studies address whether the preventive measure works (proof of concept and efficacy), late-stage prevention studies aim to prove effectiveness in different settings (for example, testing whether Pap smear screening for cervical cancer works in developing countries even though it has been proven be effective in the USA).

Whereas some research topics, such as genetic markers of cancer, are on the left side of the continuum (stages 1–2, red boxes), others — including tobacco and cancer research — often belong in the realm of prevention and policy research (stages 5–6, yellow boxes) as a large number of epidemiological studies have implicated its role in carcinogenesis. Findings derived from studies conducted in stages 1–2 are universally applicable regardless of the geographic location of the laboratory (provided that laboratory conditions are standard). However, studies become more population-specific as one moves right across the spectrum, with prevention studies being conducted in settings where the prevention strategy will be applied. Some areas of research have subtopics that span the spectrum. Studies of HPV and cervical cancer now focus on prevention and policy research (stages 5–6), however the role of nutritional status in HPV infection is a subtopic that requires basic epidemiological research (stages 1–3). As biological mechanisms of exposures that are examined in early and in aetiological epidemiological studies can be further understood with more detailed basic research, the initial stages are reversible (stages 1–3). This overall construct displays stages in chronological order and not necessarily the depth and diversity of studies required within each stage.



Training. Epidemiology research capabilities must be strengthened in non-Western regions of the world in order for global studies of cancer incidence and prevention to be sustained. Scientists in developing countries must be properly trained to allow cancer research programs to develop. This can be achieved, in part, through collaborative research, which not only allows scientists in developing countries to learn new research skills, but also allows scientists from developed nations to better understand local scientific capabilities and customs. This is important, as patient participation often depends on people's trust of local institutes and investigators. It is also important to develop programs to train new epidemiologists of developing regions, improve the interactions between scientists from developed and developing countries, and support education programs for mid-career scientists of developing nations. Ultimately, the creation of accredited graduate schools of public health and epidemiology in these countries will improve the level of research in these regions of the world.

Fair and effective collaborations. The success of research in developing countries also depends on fostering fair collaborations between investigators from developed and developing countries. One role of investigators in developed countries is to clearly define the goals of the study and to explain how findings might improve the well-being of both local and global populations. It is important for investigators to transfer knowledge and scientific skills to scientists of collaborating developing countries whenever possible. Equitable credit should also be negotiated and given to both sets of researchers in the form of shared authorships and presentations at international scientific conferences. The promotion of technologies within developing countries by local scientists should also be encouraged through technology transfer programmes supported by both private and public governmental agencies.

Bureaucracy. The large amount of bureaucracy that is often required to initiate and to carry out epidemiological studies in some countries is another impediment to research. Bureaucratic obstacles can arise from governmental regulatory agencies in both developed and developing nations. Although it is necessary to have rules to guide research practices in other countries, manoeuvring through complicated and often dated regulations can be daunting. One serious long-term consequence of overwhelming amounts of bureaucracy is that collaborative research plans are often substantially delayed or cancelled.

Issues surrounding internal study bureaucracy is another concern that can be addressed by establishing clear agreements and guidelines during the planning stages and 'oversight' or 'steering' committees. These usually consist of a group of knowledgeable researchers that are not the main study investigators, but are tangentially involved. It is important to outline which oversight or steering committees will monitor progress, and which will provide scientific and management guidance.

Ethical issues. Some studies in developing countries have been conducted without the informed consent and overview of ethical committees — either these committees were never fully established, or the subjects were uninformed of their rights and therefore were coerced into study participation. Other examples of ethical lapses in research conducted in developing countries include implementing potentially harmful interventions when subjects were not fully protected from side effects, or using coercion to improve participation. Data and samples have also been collected from people in developing counties without consent of the government or local scientists.

It is important that scientists from developing countries and their collaborators from developed countries follow international ethical regulations when conducting population-based studies (see Further information for websites for international standards for conduct of ethical research). This is not only necessary to allow researchers from developing countries to obtain recognition for contributions, but also because failure to follow these regulations can prevent subjects from participating in future studies. An important concern in the last few years has involved the unauthorized collection, export and analyses of biological samples, and the lack of benefit to local scientists and especially to local populations. Unapproved collection and shipment of biological samples is not only wrong but also hinders future endeavours and fosters mistrust. Some governments have banned the export of biological samples from their countries. In forming research collaborations with developing countries, scientists should not only outline the potential for technology transfer, but can also make provisions for some sample export permissable. As genetic analysis can be a controversial topic regardless of where it takes place, complete transparency, involving explanations of research protocols and objectives, can help address this issue.

Social issues. Investigators in developing countries are faced with unique social issues that range from cultural and gender to superstitions or concerns about being taken advantage of. Guidance from local scientists, who are most familiar with the beliefs of the population, is the best way to address most of these issues. Outreach and education programmes that familiarize communities with research can also be undertaken to improve participation, often involving local community or religious leaders.

Future directions

Developing countries have already made significant contributions to our understanding of cancer aetiology (TABLE 2). Examinations into hot-spots or exposure–disease relationships unique to specific geographic regions have advanced our knowledge of the factors that contribute to cancer risk. Developing countries often have vastly different subgroups coexisting together. Whereas some groups lead traditional lifestyles that have not changed for generations, such as in rural villages of Asia, others in urban areas of Latin America and Asia have undergone rapid changes owing to economic development. For instance, gains in women's education and improvements in nutritional status also lead to earlier menarche and later menopause in women, extending the period of hormone exposure, particularly oestrogen, which is associated with breast cancer risk. Modernization and mechanization of processes such as transportation and household chores are also resulting in reduced levels of physical activity in urban areas around the world. These forces of globalization are homogenizing lifestyles worldwide, increasing the urgency of performing epidemiological studies in developing regions.

In addition to studies of cancers typically associated with developing countries, research should expand to include other cancers, particularly those that have lower incidence rates in these areas such as lung, prostate, breast and colon cancers. Some reasons that the incidence of these cancers is low in developing regions include the lower prevalence of risk factors such as obesity. Alternatively, there could be a high prevalence of preventive factors such as increased intake of chemopreventive agents (phytoestrogens found in soy products or curcumin in spices), or higher levels of physical activity. Studying cancer in these populations is therefore an important approach to identifying possible factors that could be applied to cancer prevention worldwide.

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Competing interests statement

The authors declare no competing financial interests.

Online links

DATABASES

The following terms in this article are linked online to:

National Cancer Institute: http://www.cancer.gov/
breast cancer | cervical cancer | colon cancer | lung cancer | prostate cancer | stomach cancer

FURTHER INFORMATION

Belmont Report:
http://www.nihtraining.com/ohsrsite/guidelines/belmont.html
Declaration of Helsinki:
http://www.nihtraining.com/ohsrsite/guidelines/helsinki.html
GLOBOCAN 2000 — Cancer Incidence, Mortality and Prevalence Worldwide:
http://www-dep.iarc.fr/globocan/globocan.html
Nuremberg Code:
http://ohsr.od.nih.gov/guidelines/nuremberg.html
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http://www.nihtraining.com/ohsrsite/guidelines/45cfr46.html
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